REMARKS

Applicant has amended the specification to update related application information as requested by the Examiner. Applicant has also added to the Brief Description of the Drawings sequence identifiers of the sequences in Figure 13 as requested by the Examiner. A marked up version of the amended paragraphs in the specification, with amendments indicated by bracketing for deletions and underlining for additions, is attached hereto as Exhibit A. No new matter has been added by these amendments.

Claims 8-24 were pending in this application. Claims 13, 16 and 18 have been canceled without prejudice to Applicant's right to pursue the subject matter of any canceled claims in subsequent applications. Claims 8-12, 14-15, 17 and 19-24 have been amended to more particularly point out and distinctly claim the subject matter which Applicant regards as the invention, and new claims 25-26 have been added. Applicant retains the right to pursue the canceled subject matter in subsequent applications. Claims 8-12, 14-15, 17 and 19-26 are fully supported by the specification as originally filed, such that the above-made amendments do not constitute new matter under 35 U.S.C. § 132. Accordingly, claims 8-12, 14-15, 17 and 19-26 will be pending upon entry of this amendment. A marked up version of the amended claims, with amendments indicated by bracketing for deletions and underlining for additions, is attached hereto as Exhibit B.

The Rejections Under 35 U.S.C. § 112, Second Paragraph Should Be Withdrawn

Claims 8-12, 15, 17 and 20-22 stand rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite. Claims 8-15, 17 and 19-24 have been amended to more particularly point out and distinctly claim the subject matter which Applicant regard as the invention. Each point raised by the Examiner in Item No. 5 of the July 3, 2001 Office Action (at page 3) has been addressed in the above amendments as suggested by the Examiner, and in accordance with the requirements under 35 U.S.C. §112. As such, Applicant respectfully

submits that the rejections of claims 8-12, 15, 17 and 20-22 under 35 U.S.C. §112, second paragraph have been obviated and overcome; therefore, Applicant respectfully requests that the rejections under 35 U.S.C. §112, second paragraph be withdrawn.

The Rejections Under 35 U.S.C. § 112, First Paragraph Should Be Withdrawn

Claims 8-24 stand rejected under 35 U.S.C. §112, first paragraph as allegedly containing subject matter not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. More specifically, the Examiner states that "the claims as written read broadly on use of any nucleotide which hybridizes to SEQ ID NO:19, of any specified length or oligonucleotide composition, and further wherein the claimed treatment is of any organism for any disorder related to bcl-2 expression" (July 3, 2001 Office Action at page 4). Further, the Examiner contends that, although successful use of bcl-2 antisense compounds are found in the post-art, "such examples do not provide a representative number of species for enablement of any oligonucleotide which could hybridize to SEQ ID NO:19 to be considered a suitable candidate as a therapeutic agent for any bcl-2 related disorder in any whole organism" (July 3, 2001 Office Action at page 5).

In response, Applicant has amended all independent claims to relate to use of anticode oligomers of 10-40 bases in length for targeting human bcl-2. Support for these amendments can be found, for example, at page 11, lines 31-35 and of the original specification. Applicant respectfully submits that the above-made amendments address the Examiner's concerns regarding the use of "any oligonucleotide" for use in "any organism" such that the teachings of the original specification, coupled with the state of the art at the time of filing, provides the skilled artisan with sufficient guidance to make and use the claimed invention.

Briefly, the test for enablement is whether one skilled in the art could make and use the claimed invention, without undue experimentation, from the disclosure in the patent

specification coupled with information known in the art at the time the patent application was filed. *U.S. v. Telectronics Inc.*, 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988). Subject matter that is well known to the skilled artisan is preferably omitted from the specification. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) ("a patent need not teach, and preferably omits, what is well known in the art"). Moreover, one skilled in the art is presumed to use the available information in attempting to make and use the claimed invention. *See Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 941 (Fed. Cir. 1990) ("A decision on the issue of enablement requires determination of whether a person skilled in the pertinent art, using the knowledge available to such a person and the disclosure in the patent document, could make and use the invention without undue experimentation."). These enablement rules preclude the need for the Applicant to "set forth every minute detail regarding the invention." *Phillips Petroleum Co. v. United States Steel Corp.*, 673 F. Supp. 1278, 1291 (D. Del. 1991); *see also, DeGeorge v. Bernier*, 768 F.2d 1318, 1323 (Fed. Cir. 1985).

A disclosure adequately fulfills the enablement requirement if it defines the desired functional relationship, even if some experimentation is required. *Wilden Pump & Eng'r Co. v. Pressed & Welded Prod. Co.*, 199 U.S.P.Q. 390 (N.D. Cal. 1978), *aff'd,* 655 F.2d 984, 213 U.S.P.Q. 282 (9th Cir. 1981), *on remand*, 570 F.Supp. 224, 224 U.S.P.Q. 1074 (N.D. Cal. 1983) ("A patent's disclosure is adequate if it defines the desired functional relationship, even if some experimentation is required to reproduce the invention."). *See also, S.C. Johnson & Son, Inc. v. Carter-Wallace, Inc.*, 225 U.S.P.Q. 1022 (S.D.N.Y. 1985); *aff'd in part, vacated in part, and remanded,* 781 F.2d 198, 228 U.S.P.Q. 367 (Fed. Cir. 1986), *on remand,* 231 U.S.P.Q. 668 (S.D.N.Y. 1986) ("There is no need for a manufacturing specification. There need not be a description of every nut, bolt and detail used in the practice of the invention."); *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174 (U.S. Int'l Trade Comm. 1983), *aff'd sub nom., Massachusetts Institute of Technology v. AB*

Fortia, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985) ("[T]he fact that experimentation may be complex . . . does not necessarily make it undue, if the art typically engages in such experimentation.").

Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover,* 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in *In re Wands,* 858 F.2d 731, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the guidance provided by the specification, the presence of working examples, the amount of pertinent literature, and the level of skill in the art. The test for undue experimentation is not merely quantitative, however, since a considerable amount of experimentation is permissible, so long as it is merely routine. *Id.*

While the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of an experiment is not a consideration. Indeed, the Court of Customs and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue. *In re Angstadt,* 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). Further with respect to unpredictability, the court has specifically stated that

> Appellants have apparently not disclosed *every* catalyst which will work; they have apparently not disclosed *every* catalyst which will not work. The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with *every* species covered by a claim.
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> [S]uch a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area . . . .

Id. (emphasis in original). The *Angstadt* court went on to hold that applicants had indeed

enabled their method for catalytically oxidizing hydrocarbons, stating that

> the proposition that the disclosure must provide "guidance which will enable one skilled in the art to determine, *with reasonable certainty before performing the reaction*, whether the claimed product will be obtained" . . . is contrary to the basic policy of the Patent Act, which is to encourage disclosure of inventions and thereby to promote progress in the useful arts.
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> * * *
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> Depriving inventors of claims which adequately protect them and limiting them to claims which practically invite appropriation of the invention while avoiding infringement inevitably has the effect of suppressing disclosure.

Id., quoting and criticizing In re Rainer, 54 C.C.P.A. 1445, 377 F.2d 1006, 153 U.S.P.Q. 802 (1967) (emphasis in original).

With respect to the enablement requirement and claim scope, it is well-settled that the inclusion of undisclosed species within a broad genus does not necessarily render a claim unduly broad. *Horton v. Stevens*, 7 U.S.P.Q.2d 1245, 1247 (Bd. Pat. App. & Int'f 1988) ("The mere fact that a claim embraces undisclosed or inoperative species or embodiments does not necessarily render it unduly broad."). Inoperative species within a broad claim are clearly permissible. *Ex parte Cole*, 223 U.S.P.Q. 94, 95 (P.T.O. Bd. App. 1983) ("It is always possible to theorize some combination of circumstances which would render a claimed composition or method inoperative, but the art-skilled would assuredly not choose such a combination."); *In re Anderson*, 471 F.2d 1237, 1242, 176 U.S.P.Q. 331 (C.C.P.A. 1973) ("It is always possible to put something into a combination to render it inoperative. It is not the function of claims to *exclude* all such matters but to point out what the combination is.") (emphasis in original); *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576-77, 224 U.S.P.Q. 409, 414 (Fed. Cir. 1984) ("Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid . . . "); *Precision Metal Fabricators Inc. v. Jetstream Systems Co.*, 6 U.S.P.Q.2d 1704, 1709 (N.D. Cal. 1988) ("The enablement requirement does not require that the patent disclose the specific embodiment of the claim; a broad claim can be enabled by the disclosure of a single embodiment.") (emphasis added).

In view of the test for enablement, Applicant respectfully wishes to point out that, contrary to the Examiner's assertion that "[d]iscovery of antisense molecules with 'enhanced specificity' *in vivo* requires further experimentation for which no guidance is taught in the

specification"(July 3, 2001 Office Action at page 6), the specification teaches bcl-2 antisense compounds, synthesis of nuclease-resistant oligonucleotide backbones for bcl-2 antisense compounds, successful entry and localization of bcl-2 antisense compounds into the intended target cell and cellular compartment, use of bcl-2 antisense compounds for inhibiting bcl-2 expression *in vitro*, and methods for administering bcl-2 antisense compounds to a human (*see, e.g.*, page 14, line 16 to page 16, line 34 and Examples 13-16 of the instant specification). Importantly, the nature of antisense technology is that it involves screening of a series of antisense compounds to determine which ones have the desired antisense activity when administered to cells. As such, practitioners of this art are prepared to screen inactive antisense compounds in order to find one that demonstrates the desired antisense activity. As discussed above, enablement is not precluded by the necessity for some experimentation such as routine screening. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986).

Moreover, in contrast to the Examiner's contention that "[w]hile the specification teaches cell culture inhibition, no evidence of successful *in vivo* (whole organism) antisense inhibition has been shown, nor do the culture examples correlate with whole organism delivery," the post art convincingly demonstrates that, following the teachings of the instant specification, SEQ ID NO:17 (also known as G3139 or Genasense™) can be administered to humans to treat cancer (*see, e.g.*, Waters et al., 2000, "Phase I clinical and pharmacokinetic study of bcl-2 antisense oligonucleotide therapy in patients with non-Hodgkin's lymphoma", J Clin Oncol. 18:1812-1823; Webb et al., 1997, "BCL-2 antisense therapy in patients with non-Hodgkin lymphoma", Lancet. 349:1137-1141, attached hereto as Exhibits D and E, respectively). Furthermore, SEQ ID NO:17 is currently in clinical trials for the treatment of various human cancers (*see, e.g.*, Delihas, 2001, "Targeting the expression of anti-apoptotic proteins by antisense oligonucleotides", Curr Drug Targets 2:167-180), attached hereto as Exhibit F). Thus, to summarize, the specification teaches bcl-2 antisense oligomers, oligonucleotide modifications for improved stability, penetration into target cells, and antisense-mediated efficacy, while the post art demonstrates that *in vitro* efficacy indeed can correlate with *in vivo* efficacy. In particular, as performed by Applicant with *in vitro* experiments, antisense oligomers have been administered to humans as a simple saline solution to successfully treat human cancer (*see, e.g.*, Waters et al., 2000, "Phase I clinical and pharmacokinetic study of bcl-2 antisense oligonucleotide therapy in patients with

non-Hodgkin's lymphoma", J Clin Oncol. 18:1812-1823; Webb et al., 1997, "BCL-2 antisense therapy in patients with non-Hodgkin lymphoma", Lancet. 349:1137-1141).

The Examiner has acknowledged "isolated successes" with antisense therapy *in vivo*. Using the compositions and methods taught in the specification, the Applicant has followed the teachings of the specification to contribute to those successes *in vivo*. In particular, the teachings of the original specification with respect to the target DNA sequence, methods of making and using antisense compounds directed to the target DNA sequence, methods of making and using nuclease-resistant antisense compounds for use *in vivo*, and methods of administering such compounds *in vivo*, along with the state of the art of the time of filing and the post art successes (accomplished by following the teachings of the specification), together clearly prove enablement. As such, Applicant respectfully submits that the original specification provides adequate guidance for the skilled artisan to make and use the claimed invention. As such, Applicant respectfully submits that the rejections of claims 8-24 under 35 U.S.C. §112, first paragraph have been obviated and overcome, and therefore Applicant respectfully requests that the rejections under 35 U.S.C. §112, first paragraph be withdrawn.

CONCLUSION

Applicant respectfully requests entry of the foregoing amendments and remarks into the file of the above-identified application. Applicant believes that each ground for rejection or objection has been overcome or obviated, and that all of the pending claims are in condition for allowance. Withdrawal of all outstanding rejections and objections is therefore respectfully requested. An early allowance is earnestly sought.

Respectfully submitted,

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Enclosures